Toxicity Assessment of F-T Jet Fuel (JP-8/SPK)

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Toxicity Assessment of F-T Jet Fuel (JP-8/SPK)

- Background on major jet fuels
- Background on JP-8/SPK
- Development of the JP-8/SPK toxicity program
- Dermal Irritation
- Genotoxicity
- Inhalation
- Conclusions
- Questions

Background

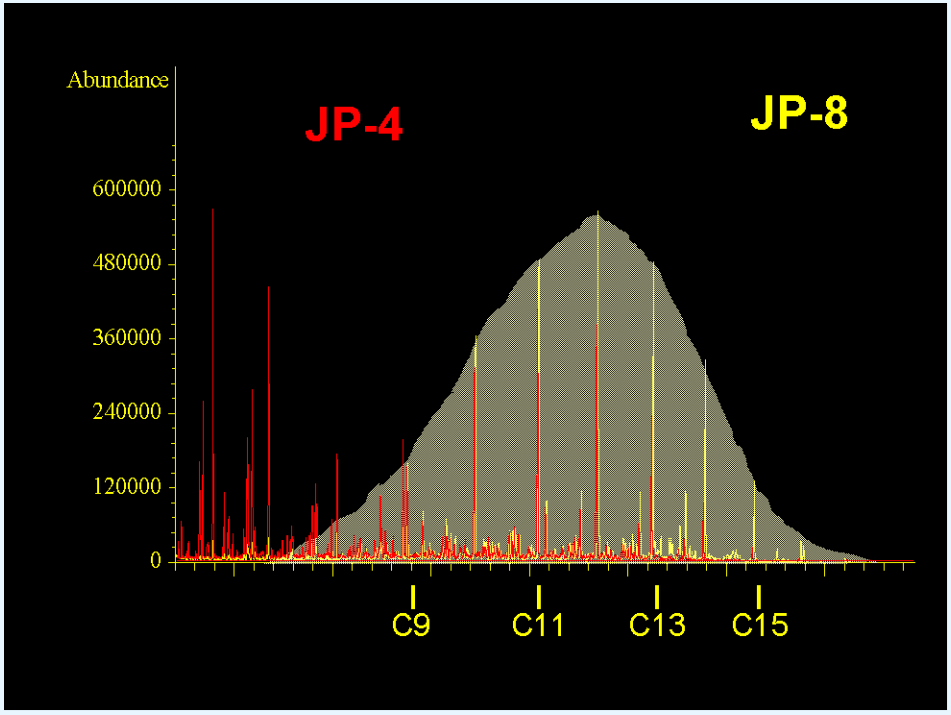
- DoD consumes ~ 5 B gallons of aviation jet fuel per year (US consumer ~25B)
- **Major Jet Fuels:**
  - Jet-A
    - Commercial
  - JP-4
    - Issued 1951
  - 50/50 kerosene-gasoline blend
  - Contains aliphatic and aromatic hydrocarbons, corrosion inhibitor and anti-static and -icing compounds
  - Phased out by USAF 1976-1996, replaced with JP-8
  - JP-5
    - US Navy Fuel
    - Primarily kerosene
    - Lower volitility

Erica Becvar
AFCEE/TDV

Background

➢ Major Jet Fuels:

- ➢ JP-8 (MIL-DTL-83133)
  - ➢ Kerosene-based replacement for JP-4
  - ➢ Mixture of aliphatic, aromatic, and substituted naphthalene hydrocarbon compounds
  - ➢ Reduced concentrations of benzene, n-hexane
  - ➢ Contains icing inhibitor, corrosion inhibitors, lubricants, and anti-static agents
  - ➢ +100 thermal stability additive can also contain metal deactivators, anti-oxidants



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John Hinz, Health Risk Assessment Support
USAF School of Aerospace Medicine

Background

- Jet fuel toxicity risks traditionally associated with aromatic hydrocarbons
  - Conventional petroleum-based military aviation fuels contain ~20%
  - Aromatics and 1-3% naphthalene.
- JP-4
  - toxicity studies have reported skin irritation, defatting, neurotoxicity nephrotoxicity and, in male rats, renal carcinogenicity.
  - In humans, symptoms of neurasthenia, psychasthenia, polyneuropathy and sexual dysfunction has been reported in military and civilian workers.

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Background

- JP-8 Toxicity
  - Considered slightly toxic
  - Oral Lethal Dose (LD_{50}) > 5.0g/kg (highest tested)
  - Dermal – non-irritating to slightly irritating
    - Repeated and continuous exposure does cause irritation in animals and humans
  - Acute Vapor Inhalation Lethal Concentration (LC_{50}) >3.43 mg/L (highest tested)
  - Acute Aerosol LC_{50} >4.39 mg/L (highest tested)
  - Subchronic Inhalation- decreased body weight and renal hydrocarbon nephrothopy in male rats
  - Chronic Inhalation – male rat nephrothapy

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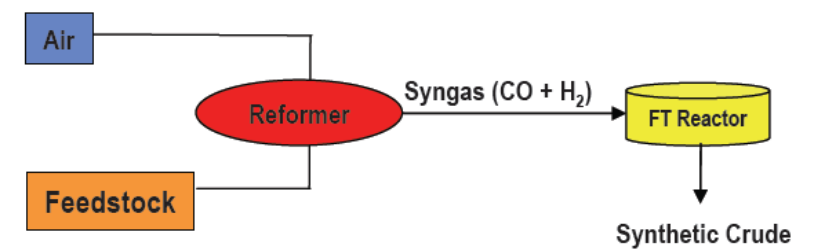
Background

- **JP-8/SPK (aka F-T, S-8…)**
  - USAF initiated the "alternative fuels" program in 1999
    - MIL-HDBK-510 Aerospace Fuels Certification
    - Goal of system certification and use of 50:50 synthetic jet fuel:JP-8 blend by 2016
  - To be used as a "drop in" fuel (JP-8:JP-8/SPK (50:50))
    - Synthetic jet fuel derived converting natural gas using coal-to-liquid (CTL) technology
    - Current synthetic jet fuels (S-8) alkane-rich, have reduced risk - essentially no aromatics or naphthalene



$(2n+1)H_2+nCO \quad C_nH_{(2n+2)}+nH_2O$

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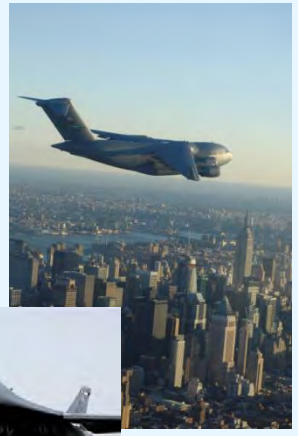
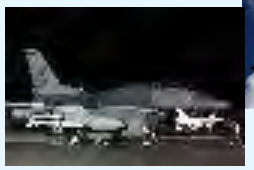
Background



- **JP-8/SPK (aka F-T, S-8…)**
  - B-52 Certification (Aug 07)
  - C-17 Ground/flight demos and FSE complete
  - F101 engine (B-1B) test at AEDC
  - CFM56 (F108) engine (KC-135) operability testing
  - B-1B Demo flight – late Spr 08
  - Acceleration of USAF Comm-Derivative aircraft certification by FAA Type-Cert (Dec 08?)
  - F-22 certification effort - complete Fall 08
  - F119 engine testing at P&W (May 08)
  - F-16, KC-135, B-2 cert planning in-process



F-T Jet Fuel Toxicity Assessment

- Funded by Air Force
- Goal - Complete initial program by end FY08
- To ensure that toxicity program addresses all issues associated with testing a complex mixture, such as jet fuel, a review panel of toxicologists was established to discuss the toxicity testing program and provide advice on testing procedures.

F-T Jet Fuel Toxicity Assessment

- **Panel members:**
  - David Mattie, Ph.D., DABT, Chair, AFRL/RHPB
  - John Hinz, AFIOH/RSRE
  - Gunda Reddy, PhD, USACHPPM
  - LT Dean Wagner, PhD, MSC, USN, NHRC/EHEL
  - David Steup, PhD, Shell Oil and Chairman of the Toxicology Committee, API
  - Errol Zeiger, Ph.D., J.D., Errol Zeiger Consulting, Chapel Hill, NC

F-T Jet Fuel Toxicity Assessment

- **Develop appropriate study design for each toxicity test proposed:**
  - *In vitro* genotoxicity tests
  - Dermal irritation test
  - Acute inhalation study
  - *In vivo* genotoxicity test in tandem with inhalation rangefinder study
  - 90-day inhalation toxicity study

F-T Jet Fuel Toxicity Assessment

- All studies are completed.
- Final analysis and/or report preparation stage.
- Occupational exposure level will be developed by the review panel for the F-T fuel during the last quarter of FY09.

F-T Jet Fuel Toxicity Assessment

➢Dermal Irritation Test

- Dermal Irritation Test
  - GLP Compliance
  - 100% concentrations of either SPK or JP-8
  - 50/50 mixture of SPK/JP-8
  - Occluded and semi-occluded exposures (each animal its own control)
  - Primary irritation index calculated to assign a descriptive rating to each test article and mixture

Dermal Toxicity

- JP-8 Occluded
- Primary Irritation Index = 2.1 Descriptive Rating = Moderately Irritating
- JP-8 Semi-Occluded
- Primary Irritation Index = 1.8 Descriptive Rating = Slightly Irritating
- SPK Occluded
- Primary Irritation Index = 2.3 Descriptive Rating = Moderately Irritating
- SPK Semi-Occluded
- Primary Irritation Index = 0.8 Descriptive Rating = Slightly Irritating
- JP-8/SPK Occluded
- Primary Irritation Index = 1.9 Descriptive Rating = Slightly Irritating
- JP-8/SPK Semi-occluded
- Primary Irritation Index = 1.5 Descriptive Rating = Slightly Irritating

F-T Jet Fuel Toxicity Assessment

In vitro genotoxicity tests

- Performed by Eurofins/ Product Safety Labs
- GLP Compliance

F-T Jet Fuel Toxicity Assessment

- **Chromosomal Aberration (CA) Test**
  - Establish potential for fuel to induce chromosomal aberrations in human lymphocytes with and without activation.

- **Conclusion**
  - Chromosomal aberrations were not induced by the fuel
  - JP8/SPK is considered to be non-clastogenic

F-T Jet Fuel Toxicity Assessment

- **Reverse Mutation Assay (Ames Test)**
- Establish potential for fuel to induce gene mutations
- Detect point mutations in *Salmonella typhimurium*
  - Histidine reversion system His^- → His^+

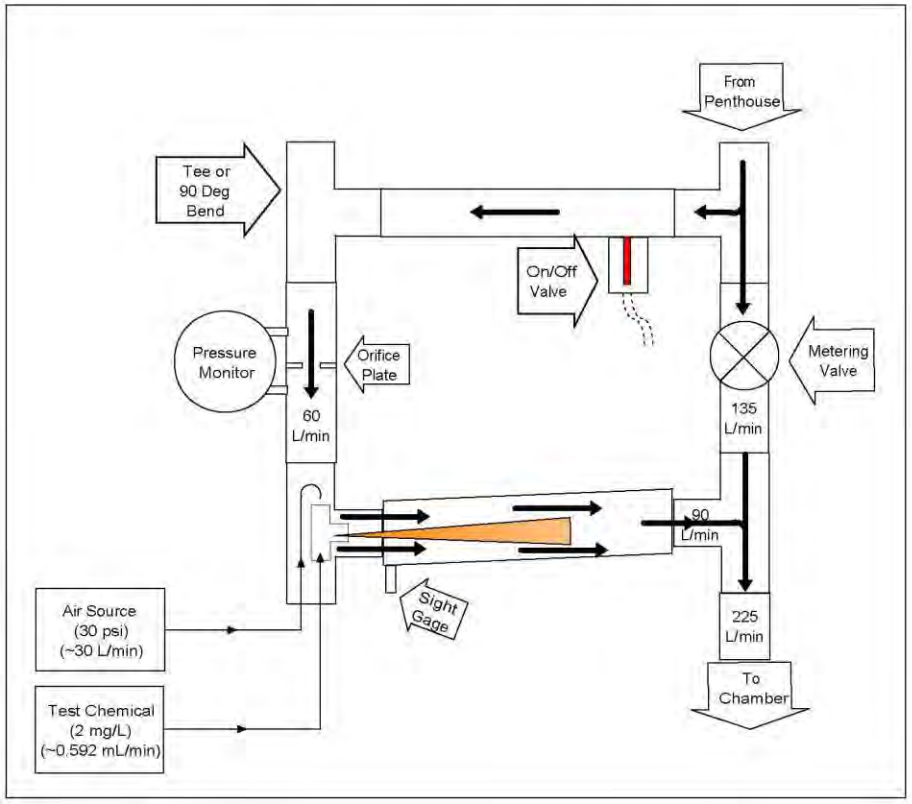
F-T Jet Fuel Toxicity Assessment

- **Reverse Mutation Assay (Ames Test)**
  - Preliminary Results
    - No toxic effects in any of five tester strains
    - No relevant increase in revertants
    - F-T jet fuel did not cause base pair or frame shift genetic mutations in any of the tester strains
- **Conclusion**
  - F-T jet fuel is considered to be non–mutagenic in this bacterial reverse mutation assay

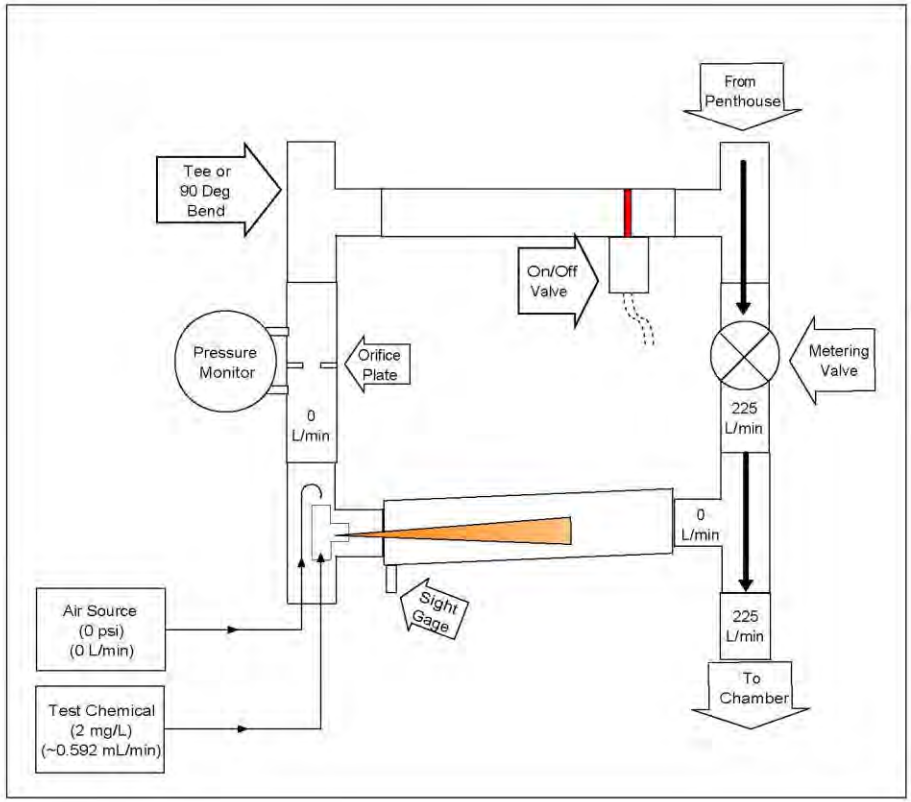
F-T Jet Fuel Toxicity Assessment

Inhalation studies

Protocol 07034: Generation of Jet Fuel: On/Off Valve in On Position



Protocol 07034: Generation of Jet Fuel: On/Off Valve in Off Position



F-T Jet Fuel Toxicity Assessment

- **Acute Inhalation Study**
  - Completed:
    - 4 hour exposure
      - 2000 mg/m^3 dose
      - 5 males/5 females
      - No clinical symptoms observed

F-T Fuel Toxicity
2-Week Study

- **2-week - Histological findings in:**
  - **lung: Inflammatory foci evident in highest doses**
  - **Olfactory epithelia: degeneration in highest doses**
  - **Kidney: hyaline droplet accumulation in all males exposed**
  - **Liver: Panlobular hepatocyte changes in all males exposed and females exposed to the highest concentration**

F-T Jet Fuel Toxicity Assessment

- 90-day Inhalation Study
  - Study design based on:
    - U.S. Environmental Protection Agency (U.S. EPA) Harmonized Test Guideline developed by the Office of Prevention, Pesticides and Toxic Substances (OPPTS) 870.3465 90-Day Inhalation Toxicity and
    - Organization for Economic Cooperation and Development (OECD) guideline 413, Subchronic Inhalation Toxicity:
    - 90-day Study
    - U.S. EPA Health Effects Test Guideline OPPTS 870.6200 Neurotoxicity Screening Battery.

F-T Jet Fuel Toxicity Assessment

- 90-day Inhalation Study
- Started April 28
  - Route, Duration and Frequency of Administration
    - Test substance will be administered as aerosol/vapor combination for 6 h/d, 5 d/w for 13 w
  - Exposure Levels
    - Animals will be exposed to three concentrations, high, intermediate and low, with a control group (0 mg/mm^3).
      - 2000 mg/m^3, 700 mg/m^3 and 200 mg/m^3

F-T Jet Fuel Toxicity Assessment

- 90-day Inhalation Study
  - Observations
    - Animals will be observed before and after exposures for overt signs of toxicity
    - Tissues and organs will be examined for gross pathology
    - Blood will be collected for clinical pathology
    - Tissues collected for histopathology including:
      - Nasal airways, trachea, larynx, lungs, liver, kidney, spleen, adrenals, heart and others

F-T Jet Fuel Toxicity Assessment

- 90-day Inhalation Study
  - Motor Activity and Functional Observational Battery
    - To assess the neurobehavioral effects
  - Sperm Morphology and Vaginal Cytology Examinations
    - Sperm will be stained and examined for percentage of abnormal sperm
    - Alterations in the estrous cycle will be assessed by examination cytology from vaginal smears

F-T Jet Fuel Toxicity Assessment

90-day Inhalation Study

Group	Exposure Level	Number of Animals	
	mg/m^3	Males	Females
Control Replicate 1	0	5	5
Control Replicate 2		5	5
Low Replicate 1	200	5	5
Low Replicate 2		5	5
Intermediate Replicate 1	700	5	5
Intermediate Replicate 2		5	5
High Replicate 1	2000	5	5
High Replicate 2		5	5
Total		40	40

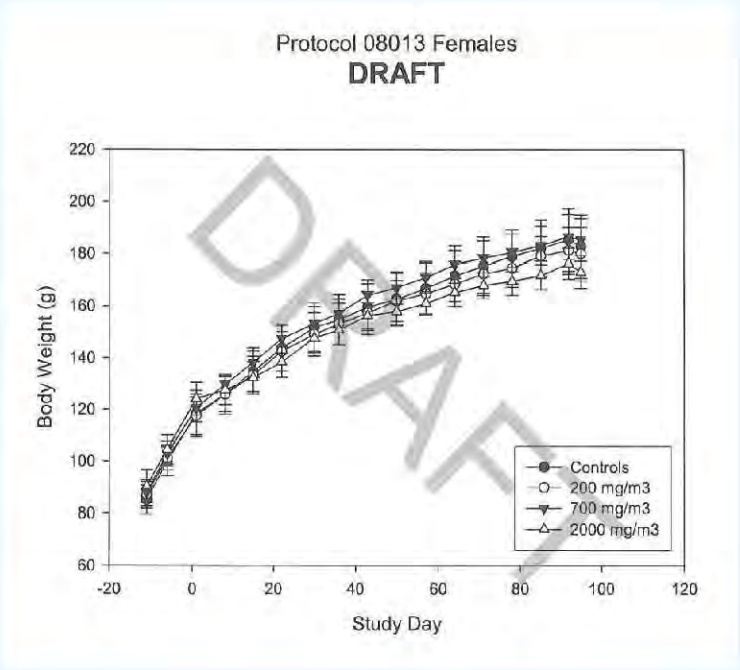
90-Day Inhalation Study

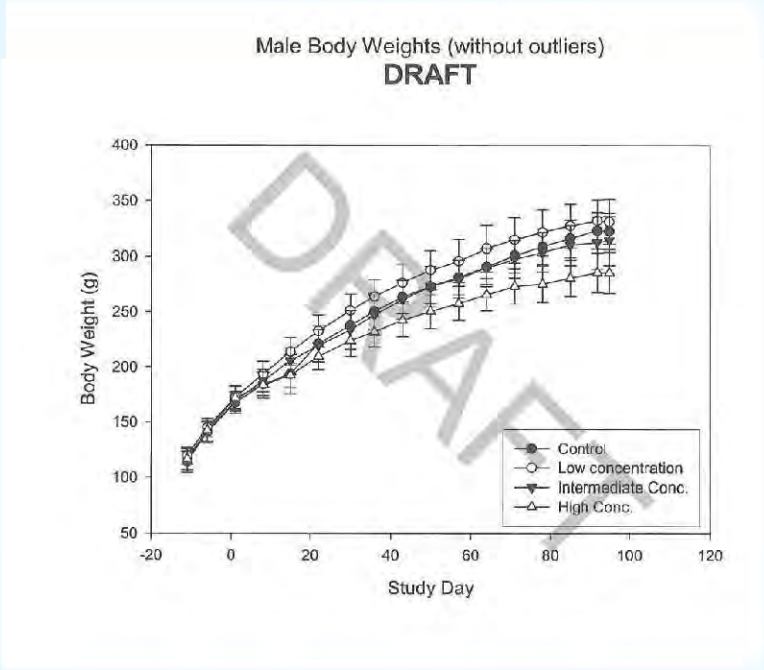
- Observations
  - Animals observed before and after exposures for overt signs of toxicity
  - Tissues and organs examined for gross pathology
  - Blood collected for clinical pathology
  - Full tissue list collected for histopathology
    - Analyzed male rat kidneys for alpha 2 microglobulin

90-Day Inhalation Study
Mean Exposure Levels

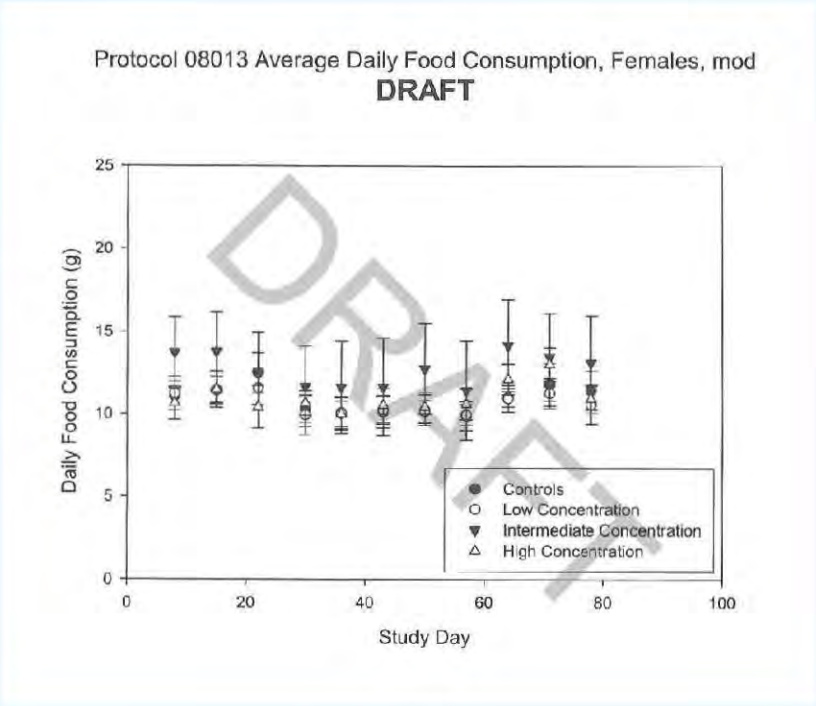
Group	Exposure Level	Number of Animals	
		Males	Females
Control	0.02 ± 0.10	10	10
Low	200.1 ± 5.0	10	10
Intermediate	698.6 ± 16.8	10	10
High	1988.4 ± 48.1	10	10

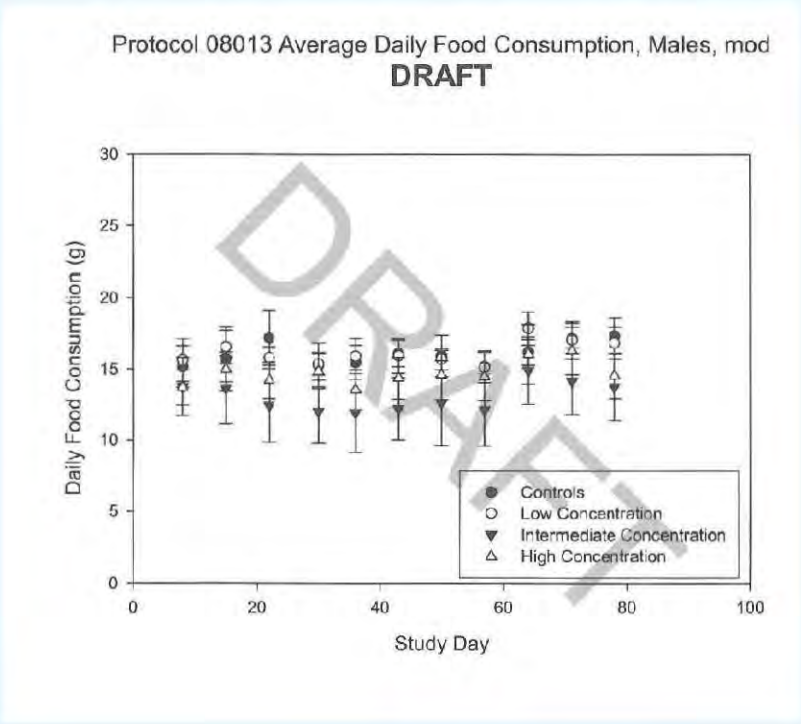
Body Weights





Food Consumption





Hematology

- There were no biologically significant or toxicologically significant changes in hematology or clinical chemistry values seen in any of the groups.

Nasal Histopathology

Table 3 Incidence of selected findings in the noses of male rats (ten per group)

Group	Olfactory Epithelial Degeneration	Hypertrophy Hyperplasia Goblet Cells Nasopharngeal Duct
Control	0	0
Low	0	0
Intermediate	9	10
High	10	10

Table 4 Incidence of selected findings in the noses of female rats (ten per group)

Group	Olfactory Epithelial Degeneration	Hypertrophy Hyperplasia Goblet Cells Nasopharngeal Duct
Control	0	0
Low	0	0
Intermediate	8	9
High	10	10

Lung Histopathology

Table 5 Incidence of Inflammatory Cell Infiltration in the lungs of male rats (ten per group)

Group	Multifocal Inflammatory Cell Infiltration	Focal Inflammatory Cell Infiltration
Control	0	0
Low	0	1
Intermediate	0	1
High	10	0

Table 6 Incidence of Inflammatory Cell Infiltration in the lungs of female rats (ten per group)

Group	Multifocal Inflammatory Cell Infiltration	Focal Inflammatory Cell Infiltration
Control	0	0
Low	0	0
Intermediate	0	3
High	10	0

Kidney Histopathology

Table 7 Incidence of selected findings in the kidneys of male rats (ten per group)

Group	Increased Hyaline Droplet Tubular Epithelium
Control	0
Low	0
Intermediate	0
High	10

Alpha 2 Microglobulin

Group	Exposure Level	$\alpha_{2\mu}$ - globulin Concentration (µg/mg)	
		Males	Females
Control	0.02 ± 0.10	49.43 ± 20.87	0.16 ± 0.05
Low	200.1 ± 5.0	49.72 ± 20.57	N/A
Intermediate	698.6 ± 16.8	50.90 ± 13.72	N/A
High	1988.4 ± 48.1	35.65 ± 8.49	0.15 ± 0.01

F-T Jet Fuel Toxicity Assessment

Conclusions:

- Dermal - animal protocol approved, start date TBD
- Genotox - No genetic mutations observed in vitro
- Inhalation
  - Acute - No clinical symptoms observed
  - 2-week - Histological findings in:
    - lung: Inflammatory foci evident in highest doses
    - Olfactory epithelia: degeneration in highest doses
    - Kidney: hyaline droplet accumulation in all males exposed
    - Liver: Panlobular hepatocyte changes in all males exposed and females exposed to the highest concentration
  - 90-day- Started 28 Apr 08

F-T Jet Fuel Toxicity Assessment

Next:

- **Develop HHA**
- **Sensory Irritation Assay**
- **Genetic Biomarkers of Exposure**
- **Immunotoxicity Screen**


Questions?